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Award Number: W81XWH-10-1-0699

TITLE:Randomized Phase II Trial of Adjuvant WT-1 Analog Peptide Vaccine
in Patients with Malignant Pleural Mesothelioma after Completion of
Multimodality Therapy

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REPORT DATE: September 2014

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

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REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
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1. REPORT DATE (DD-MM-YYYY) September 2014		2. REPORT TYPE Annual		3. DATES COVERED (From - To) 15 Aug 2013 - 14 Aug 2014	
4. TITLE AND SUBTITLE TITLE:Randomized Phase II Trial of Adjuvant WT-1 Analog Peptide Vaccine in Patients with Malignant Pleural Mesothelioma after Completion of Multimodality Therapy				5a. CONTRACT NUMBER	
				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER W81XWH-10-1-0699	
6. AUTHOR(S) Lee M. Krug, M.D. GO CKN ² ntwi rB o uneeQti				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Sloan-Kettering Institute for Cancer Research New York, NY 10065				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for public release; distribution unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT The Wilms' tumor gene, WT1, encodes transcription factors that regulate cell proliferation, differentiation, and apoptosis. WT1 protein is highly expressed in malignant pleural mesothelioma (MPM), and is a rational target for immunotherapy. We have developed a vaccine comprised of four WT1 heteroclitic peptides that are given together with Montanide and GM-CSF as immunologic adjuvants. This WT1 vaccine was previously tested in a pilot trial, and shown to be safe and immunogenic. We are now testing the efficacy of this vaccine in MPM patients who have minimal disease burden after completion of multimodality therapy, but remain at exceedingly high risk for recurrence. The specific aim of this project is to conduct a multicenter, blinded, randomized trial comparing treatment with the WT-1 peptide vaccine + Montanide/GM-CSF to treatment with Montanide/GM-CSF alone in patients with MPM who have completed multimodality therapy. The primary endpoint is progression free survival. The trial is open at Memorial Sloan-Kettering and MD Anderson Cancer Center and is actively accruing.					
15. SUBJECT TERMS Mesothelioma, WT1, vaccine					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT UU	18. NUMBER OF PAGES 6	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U			19b. TELEPHONE NUMBER (include area code)

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INTRODUCTION:

The Wilms' tumor gene, WT1, encodes transcription factors that regulate cell proliferation, differentiation, and apoptosis. WT1 protein is highly expressed in malignant pleural mesothelioma (MPM), and is a rational target for immunotherapy. We have developed a vaccine comprised of four WT1 heteroclitic peptides that are given together with Montanide and GM-CSF as immunologic adjuvants. This WT1 vaccine was previously tested in a small pilot trial, and shown to be safe and immunogenic. We have chosen to test the efficacy of this vaccine in MPM patients who have minimal disease burden after completion of multimodality therapy, but remain at exceedingly high risk for recurrence. The specific aim of this project is to conduct a multicenter, double-blinded, randomized trial comparing treatment with the WT-1 peptide vaccine + Montanide/GM-CSF to treatment with Montanide/GM-CSF alone in patients with MPM who have completed multimodality therapy. The primary endpoint is progression free survival.

BODY:

This project has proceeded as indicated in the approved Statement of Work:

- The peptides were purchased, manufactured, and underwent sterility testing.
 - The peptides were ordered from AmbioPharm, Inc. Once produced, they were vialled under GMP conditions by University of Iowa Pharmaceuticals. The investigational agent completed sterility and stability testing to ensure safety for human use. The vials were delivered to the pharmacy at MSKCC.
- The protocol was reviewed by the various committees at MSKCC and the DOD leading to IRB approval.
 - After IRB approval in September, 2010, the study received approval from the FDA on 12/21/2010. During that time, the protocol was reviewed by the HRPO at the Department of Defense and several comments were made requiring changes to the protocol. The requested changes were made, reviewed by HRPO, and an amendment to the protocol was submitted to the IRB. The amendment was approved on 2/9/11. Final review took place by HRPO and an approval memo was issued on 2/11/11.
 - A start-up meeting was held with the research staff on 2/1/11 to inform all of the participants about the rationale, design, and logistics of this study.
- M.D Anderson Cancer Center received IRB approval for the protocol in August, 2012, but they were unable to enroll their first patient until April, 2013 due to delays related to institutional processes, and FDA and DOD approvals.
- Additional sites have not yet been recruited for participation in the study due to budget constraints.

KEY RESEARCH ACCOMPLISHMENTS:

- The planned randomized phase II trial is open at MSKCC and MDACC and is actively accruing patients. 28 patients have been enrolled including 23 from MSKCC and 5 from MDACC. No treatment related adverse events have occurred.

- An interim analysis was conducted based on data as of January 24, 2014. As of that date, 22 patients had registered on trial, 18 patients MSKCC, 4 patients at MD Anderson. Data were unblinded only to the biostatistician to examine the early stopping criteria for each arm separately. The first 10 patients in each arm were examined. Incomplete follow-up was available to make a decision to stop the trial, and continuation was recommended.
- MSKCC has entered a licensing agreement for the WT1 vaccine with SELLAS Life Sciences Group (<http://www.prnewswire.com/news-releases/sellas-life-sciences-group-signs-exclusive-license-agreement-for-global-rights-on-development-and-commercialization-of-wt1-cancer-vaccine-with-memorial-sloan-kettering-cancer-center-273987461.html>). This may help facilitate additional sites to open this trial, which would increase accrual.

REPORTABLE OUTCOMES:

This protocol was highlighted in several presentations which have increased exposure and enrollment. This includes:

ASCO 2011, Chicago, IL - poster presented at Trials in Progress Session
World Conference on Lung Cancer, Amsterdam, Jul 2011, slide presentation
Meso Foundation Symposium Jul 2011 and Jul 2012, Washington DC
<http://www.youtube.com/watch?v=VNUXss6B2uY>

Meso Foundation Podcast, Feb 23, 2012.

Meso Foundation conference at University of Pennsylvania

CONCLUSION:

The clinical trial is open to enrollment at Memorial Sloan-Kettering and MD Anderson which will continue for the next two years. The rate of accrual is slower than expected due to the delays in getting MD Anderson open. A no-cost extension of the grant will be considered. We are also exploring the possibility of opening additional sites.

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vaccine as adjuvant therapy in patients with malignant pleural mesothelioma. J Clin Oncol 29: 2011 (suppl; abstr TPS139)

APPENDICES:

None

SUPPORTING DATA:

None